FDA Briefing Document

Oncologic Drugs Advisory Committee

February 9, 2012

NDA: 21790
Decitabine (Dacogen)
Eisai, Inc.

DISCLAIMER STATEMENT

The attached documents contain background material prepared by the Food and Drug Administration (FDA) for the panel members of the Advisory Committee (AC). The FDA background package often contains assessments and/or conclusions and recommendations written by individual FDA reviewers. Such conclusions and recommendations do not necessarily represent the final position of the individual reviewers, nor do they necessarily represent the final position of the Review Division or Office. We have brought the Dacogen NDA with the applicant proposed indication "for the treatment of acute myelogenous leukemia (AML) in adults ≥ 65 years of age who are not considered candidates for induction chemotherapy" to this Advisory Committee in order to gain the Committee's insights and opinions. This background package may not contain all issues relevant to the final regulatory recommendation and instead is intended to focus on issues identified by the Agency for discussion by the advisory committee. The FDA will not issue a final determination on the issues at hand until input from the advisory committee process has been considered and all internal reviews have been finalized. The final determination may be affected by issues not discussed at this meeting.

This document is based on the applicant's information as provided up to May 6, 2011.

TABLE OF CONTENTS

Listing of Abbreviations

AML	Acute myelogenous leukemia
BM	Bone marrow
BSC	Best supportive care
CI	Confidence interval
CR/CRp	Complete remission / Complete remission without platelet recovery
CSR	Clinical study report
TC	Treatment choice
ECOG	Eastern Cooperative Oncology Group
FAB	French-American-British
IV, i.v.	Intravenous
ITT	Intent to treat
HR	Hazard ratio
LDAC	Low dose cytarabine
MDS	Myelodysplastic syndromes
NDA/sNDA	New drug application /new drug application supplement
OS	Overall survival
PS	Performance status
SEER	Surveillance epidemiology and end results
TEAE	Treatment emergent adverse event
WHO	World health organization

Listing of Tables

Listing of Figures

All tables and figures were created by the FDA unless otherwise indicated.

1. Applicant's Proposed Indication

Dacogen is indicated for treatment of acute myelogenous leukemia (AML) in adults ≥ 65 years of age who are not considered candidates for induction chemotherapy.

2. Executive Summary

This NDA submission is based on results of a randomized study, DACO-016, supported by a single arm study DACO-017. The study DACO-016 was a randomized, controlled, open-label, multicenter trial comparing decitabine (20 mg/m^2 i.v., Days 1-5, every 4 weeks) to control treatments as first line therapy for AML in patients age 65 years or older. The control treatments (TC) were either low dose cytarabine (LDAC, 20mg/m^{2,} subcutaneously (s.c.), Days 1-10, every 4 weeks) or best supportive care (BSC). The primary endpoint was overall survival.

Efficacy:
The Applicant proposed a final analysis of overall survival (OS) based on 385 events. The final analysis of overall survival was based on 396 events. The observed median overall survival times were 7.7 months for the decitabine arm and 5.0 months for the control arm, with a hazard ratio of 0.85 (95% CI 0.69-1.04, p=0.11). After final analysis cut-off, the Applicant collected an additional one year follow-up survival data and performed an ad hoc analysis at 92% events, of which the median OS of either treatment arm was unchanged, but with a hazard ratio of 0.82 (95% CI 0.68-0.99, nominal p=0.04).

Safety
The safety profile of decitabine was comparable to that described in previous studies in MDS patients. However, a higher incidence of treatment emergent adverse events occurred in AML patients who received decitabine treatment as compared to the control group. Common adverse events included thrombocytopenia, infection, anemia, febrile neutropenia and neutropenia.

Issue with the Submission

The study failed to demonstrate benefit based on statistical interpretation. Given that overall survival is the gold standard, we ask the Oncologic Drugs Advisory Committee to discuss the risks and benefits of Dacogen for the treatment of newly diagnosed AML in patients 65 and older.

3. Background

3.1 Use of standard induction chemotherapy for elderly AML patients

Although AML can present at any age, the median age for AML at diagnosis is 69 years in US (SEER). Elderly patients with AML are under-represented in studies of AML

therapies. Retrospective population analyses by Menzin et al.[1] indicated an inverse relationship between age and likelihood of receiving induction or palliative chemotherapy (Table 1).

Table 1: Relationship between age and likelihood to receive standard induction chemotherapy

Age	**65-74 years (N=1,132)**	**75-84 years (N=1,082)**	**≥85 years (N=433)**	**Total (N=2,657)**
Received chemotherapy	44%	24%	6%	30%

Source: Menzin et al. 2002.

Elderly patients have more comorbidities, often have poorer performance status at the time of diagnosis, less tolerance to intensive chemotherapy, and therefore less likely judged to be fit for standard induction therapy. Reduced tolerability is multifactorial and can be affected by duration and severity of treatment-induced myelosuppression, gastrointestinal mucositis, baseline organ dysfunction, and poor performance status. Only about 30% of 3439 patients who were 65 or older and identified by Medicare claims, received some form of chemotherapy.[1,2]

A high rate of early treatment-related mortality is a major contributor to the lower survival rates observed in elderly patients with AML. Treatment-related mortality in elderly patients with poor-risk AML may be as high as 25%. In a study of patients at least 80 years of age, the mortality rate at 1 month was 48% and CR rate was less than 30%. As a result, elderly patients with AML often are offered palliative treatments or supportive care alone. For such patients, the benefit-risk ratio of conventional cytotoxic chemotherapy was expected to be low; and they were not usually considered as optimal candidates to receive standard induction chemotherapy, as shown in table below.[1, 3-11]

Table 2: Comparison of outcome for different age groups

Outcome	**< 65**	**≥65**
Treatment related death	10-20%	25% - 48%
Survival	15% ≥ 3 years	< 6% at 2 years

Source: Menzin et al. 2002.

3.2 Acceptable treatment options for elderly AML patients who are not fit for standard induction therapy

In United States, the commonly accepted treatment options for elderly patients who are not fit for standard induction therapy are intermediate intensity chemotherapy, low dose cytarabine (LDAC), azacitidine, best supportive care, and clinical trial. Low dose cytarabine was superior to Best Supportive Care or hydroxyurea in achieving CR in elderly, less fit AML patients.[10]

3.3 Relevant regulatory issues in AML induction therapy developments

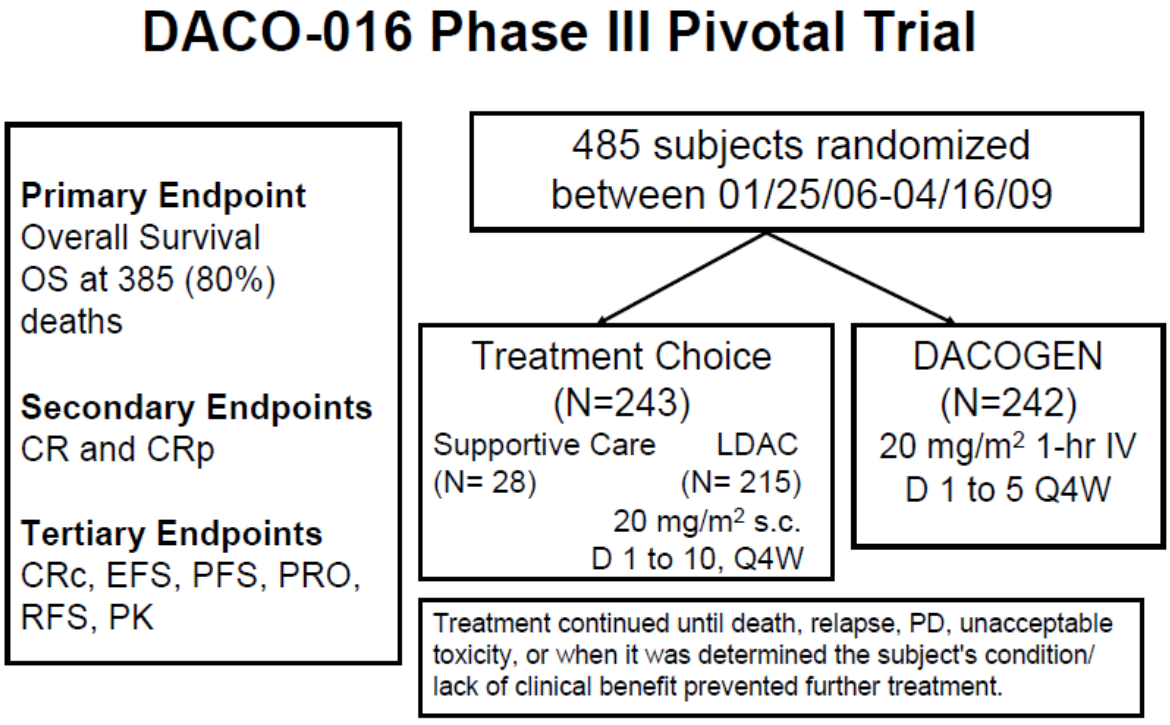
Previous FDA approvals in the treatment of AML in adult patients have been based on Phase III randomized trials (the combination of daunorubicin plus cytarabine or idarubicin plus cytarabine) in which complete remission rates and overall survival were used as endpoints.

4. Design and Enrolment of Study DACO-016

4.1 Study DACO-016 Design

Study DACO-016 was an open-label, randomized, multi-center study. A total of 485 subjects were randomized 1:1 to receive either Dacogen (n= 242) or Treatment choice (n= 243) which included a patients' choice with physician's advice of low-dose cytarabine (n=215) or supportive care (n= 28). The randomization was stratified by age (65-69 vs. ≥ 70 yrs), ECOG performance status (0-1 vs. 2), and cytogenetic risk (poor vs. intermediate).

Figure 1: Study DACO-016 Design.



CR=complete remission; CRc=cytogenetic CR; D=Day; EFS=event-free survival; hr=hour; IV=intravenously; LDAC=low-dose cytarabine; PD=progressive disease; PFS=progression-free survival; PK=pharmacokinetics; PRO=patient-reported outcomes; Q4W=every 4 weeks; RFS=relapse-free survival; s.c.=subcutaneously
Source: Clinical reviewer's figure based on the DACO-016 CSR

The eligible patients were age 65 years or older, newly diagnosed with de novo or secondary AML by WHO criteria, with poor risk or intermediate risk cytogenetics by Southwest Oncology Group criteria, ECOG performance status 0-2, adequate organ function and free of infection. Patients were to be excluded with any of the following: favorable cytogenetics, any prior therapy (except hydroxyurea) and active infection under parental antibiotic treatment. However, patients who were suitable for standard induction therapy were not specifically excluded from the study. Approximately 480 patients were to be enrolled in DACO-016.

The primary objective of the trial was to compare the overall survival (OS) in patients who were randomized to receive Dacogen or control treatment. For the primary endpoint, two interim analyses for futility and one final analysis of OS were planned:

- 1st interim analysis at 1/3 expected # of events (~128 deaths)
- 2nd interim analysis at 2/3 expected # of events (~257 deaths)
- Final analysis at total expected # of events (~385 deaths)

The significance level for the final analysis of OS was 0.0462 (2-sided) after adjusting for 2 interim analyses with Lan-Demets alpha spending function and the O'Brien-Fleming stopping boundaries. According to the trial design parameters, a final analysis of OS based on 385 deaths (events) will have 80% power to detect a 25% reduction in mortality risk, i.e. a hazard ratio of 0.75 for Dacogen vs. TC arm (median overall survival of 8 months and 6 months for Dacogen and TC arm respectively).

The secondary endpoints included overall remission rate (OR, CR+CRp) and safety.

4.2 Study DACO-016 enrollment

DACO-016 enrolled 485 patients from 65 international sites and randomized 242 and 243 patients to the Dacogen arm and TC arm, respectively. The demographics and disease characteristics are summarized as follows.

Table 3: Study DACO-016 patient demographic

Parameter	Dacogen N= 242	TC N= 243
Age (median- years)	73	73
- Age <65	3 (1.2)	1 (0.4)
- Age 65- 69 years (%)	68 (28)	69 (28)
- Age ≥ 70 (%)	171 (71)	173 (71)
Sex – n (%)		
- Male	137 (57)	151 (62)
- Female	105 (43)	92 (38)
Race - n (%)		
- White	209 (86)	213 (88)
- Black	0 (0)	3 (1.2)
- Asian	33 (14)	27 (11)
ECOG PS - n (%)		
- ECOG PS = 0	42 (17)	47 (19)
- ECOG PS = 1	140 (58)	131 (54)
- ECOG PS = 2	60 (25)	65 (27)

Source: sNDA 21790, CSR Page# 76 table 9

Table 4: Study DACO-016 patient disease characteristics

AML characteristics	**Dacogen N= 242**	**TC N= 243**
Median time from AML diagnosis to randomization (days)	14 (3.0, 346)	15 (0.0, 398)
Type AML – n (%)		
- De novo AML	155 (64)	158 (65)
- Secondary AML	87 (36)	85 (35)
FAB classification – n (%)		
- M0	17 (7)	21 (8.6)
- M1	48 (19.8)	56 (23)
- M2	102 (42.1)	100 (41.2)
- M4	46 (19)	38 (15.6)
- M4EO	1 (0.4)	0
- M5	11 (4.5)	9 (3.7)
- M6	8 (3.3)	5 (2.1)
- M7	1 (0.4)	2 (0.8)
- Not applicable to FAB class	3 (1.2)	5 (2.1)
- Unknown	6 (2.5)	6 (2.5)
Blasts in BM (%) – n (%)		
- <20%	4 (1.7)	8 (3.3)
-20-30%	65 (27)	58 (24.1)
- >30-50%	67 (27.8)	74 (30.7)
- > 50%	105 (43.6)	101 (41.9)
Cytogenetic classification of risk – n (%)		
- Intermediate	165 (68)	164 (67)
- Poor	77 (32)	79 (33)
Chromosome alterations – n (%)		
- Normal karyotype (%)	116 (48.9)	108 (45)
- +8	24 (10.1)	31 (12.9)
- Abnormal 11q23	4 (1.7)	2 (0.8)
- t(3;3)	1 (0.4)	0
- 5	3 (1.3)	10 (4.2)
- del(5q)	16 (6.8)	9 (3.8)
- 7	11 (4.6)	19 (7.9)
- del(7q)	3 (1.3)	4 (1.7)
- Complex (≥3) abnormalities	64 (27.0)	60 (25.0)
- Other abnormalities	40 (16.9)	50 (20.8)

Source: sNDA CSR Page #78 – 79 Tables 10 and 11.

Table 5: Study DACO-016 patient baseline hematology parameters

Feature	Dacogen N= 242	TC N= 243
Peripheral blasts		
N	162	166
Category, n (%)		
- <20%	93 (57.4)	72 (43.4)
- 20- 30%	14 (8.6)	22 (13.3)
- >30- 50%	18 (11.1)	32 (19.2)
- > 50%	37 (23)	40 (24)
Median % of blasts in PB (range)	16.0 (1,94)	22.5 (1,94)
Hemoglobin (g/dL)		
N	237	236
Category, n (%)		
- < 6.5 g/dL (%)	5 (2.1)	3 (1.3)
- 6.5 - < 8 g/dL	32 (13.5)	28 (11.9)
- 8 - < 10 g/dL (%)	129 (54.4)	131 (55.5)
- ≥ 10 g/dL	71 (30)	74 (31.4)
Median Hb g/dL (range)	9.3 (5.2,15)	9.4 (5,12.6)
ANC (absolute neutrophil count)		
N	226	232
Category, n (%)		
- < 500 cells /µL	97 (42.9)	106 (45.7)
- 500- < 1000 /µL	42 (18.6)	34 (14.7)
- 1000- <1500 /µL	25 (11.1)	23 (9.9)
- ≥1500 /µL	62 (27.4)	69 (29.7)
Median neutrophils (thousand) /µL (range)	0.60 (0.0,19.6)	0.62 (0.0,48.3)
Platelet count		
N	225	213
Category, n (%)		
- <25,000	40 (17.8)	34 (16)
- 25,000- <50,000 /µL	61 (27.1)	71 (33.3)
- 50,000- <75,000 /µL	40 (17.8)	34 (16)
- ≥ 75,000 /µL	84 (37.3)	74 (34.7)
Median platelets (thousand) /µL (range)	58 (6,487)	50 (6,490)
WBC (white blood cell)		
N	237	236
Category, n (%)		
- < 1,000	25 (10.5)	22 (9.3)
- 1,000- < 2,000	46 (19.4)	50 (21.2)
- 2,000- <3,000	44 (18.6)	31 (13.1)

Feature	Dacogen N= 242	TC N= 243
- 3,000- < 4,000	18 (7.6)	18 (7.6)
- 4,000- <10,000	48 (20.3)	59 (25)
- ≥ 10,000	56 (23.6)	56 (23.7)
Median white blood cells (thousand) /µL (range)	3.10 (0.3,127)	3.69 (0.5,80.9)

Source: sNDA CSR Page #81 Tables 13.

5. Major efficacy issue and findings

The primary endpoint of study DACO-016 was not met. The study failed to demonstrate a statistically significant improvement in the primary endpoint of OS when patients were treated with Dacogen comparing to treatment with Treatment Choice (TC). From a statistical point of view, any further analyses on OS, any other endpoints, or within any subgroup are exploratory (see Section 5.1).

5.1 Pre-Specified Efficacy Analysis

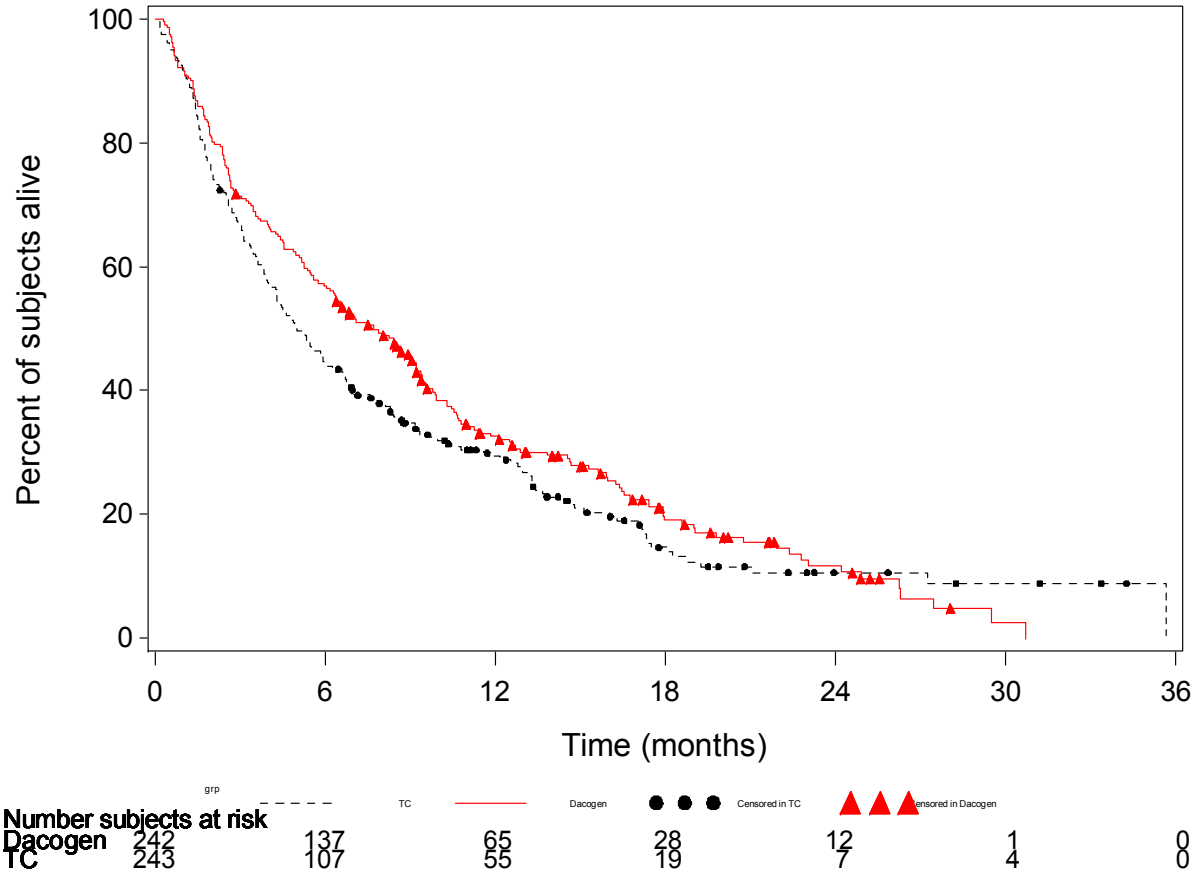
The study cut off for the final analysis of OS was on October 28, 2009 by which 396 deaths had occurred. The stratified log-rank test and stratified Cox regression model were used to compare OS between the two treatment arms and calculate the observed hazard ratio, respectively. Primary analysis results for OS are summarized in Table 6 and Figure 5. The observed difference was not statistically significant (nominal p-value=0.11). The Dacogen versus TC hazard ratio was 0.85 with estimated median OS of 7.7 months and 5.0 months for the Dacogen and TC arms, respectively.

Table 6: OS – primary analysis results (Cutoff of October 28, 2009)

	Dacogen (N=242)	TC (N=243)
Deaths (%)	197 (81.4%)	199 (81.9%)
Median OS (months) (95% CI)	7.7 (6.2, 9.2)	5.0 (4.2, 6.3)
Nominal P value	0.11	
Stratified Hazard Ratio (95% CI)	0.85 (0.69, 1.04)	

Source: sNDA CSR Page #89 Table 18.

Figure 2: Kaplan-Meier estimation for OS (ITT, cutoff of October 28, 2009)



Source: Statistical reviewer's figure based on the DACO-016 CSR Page #90 Figure 3.

Upon failing to achieve statistical significance at either interim analyses or the final analysis, all "alpha" has been spent. There are no further formal statistical comparisons to be performed.

5.2 OS results across geographic region

Table 7 summarizes the study accrual by geographic region. Among all subjects, 9.9% were enrolled from the United States (US). Note, a smaller percentage of subjects in the TC arm compared with the Dacogen arm (14.0% vs. 21.1%) was from Western Europe.

Table 7: Study accrual by geographic region

Geographic Region	**Dacogen (N=242) n (%)**	**TC (N=243) n (%)**
North America	35 (14.5)	69 (19.3)
United States	21 (8.7)	27 (11.1)
Australia	16 (6.6)	22 (9.1)
Asia	31 (12.8)	27 (11.1)
Eastern Europe†	109 (45.0)	113 (46.5)
Western Europe*	51 (21.1)	34 (14.0)

† Includes Czech Republic, Hungary, Poland, Romania, Russian Federation, and Serbia

* Includes France and Spain

Source: FDA statistical reviewer's analysis

Table 8 provides the results from exploratory analyses of OS by geographic region. There is great variability across geographic region in the difference in median OS. Additionally, a smaller percentage of subjects in the control arm (14.0% vs. 21.1%) were from Western Europe, where median survival was longer. This imbalance and differences in median survival across region may contribute to over estimating the difference in median survival between treatment arms in the overall population. Adjusting for geographic region in the OS analysis for the overall population yielded a p-value of 0.22 and a hazard ratio of 0.87 (95% CI (0.70, 1.08)). In this exploratory analysis inconsistency with respect to hazard ratios among the regions are observed.

Table 8: Results of OS by geographic region (Cutoff of October 28, 2009)

Region	Dacogen		TC		Difference in Medians (mos.)	HR
	Event/ N	Median (mos.)	Event/ N	Median (mos.)		
North America	30/35	7.1	43/47	4.2	2.9	0.78
United States	20/21	4.6	26/27	4.8	-0.2	0.97
Australia	15/16	4.7	20/22	9.2	-4.5	1.77
Asia	23/31	9.3	23/27	4.5	4.8	0.83
Eastern Europe	89/109	6.7	91/113	4.3	2.4	0.73
Western Europe	40/51	9.1	22/34	14.4	-5.3	1.43

Source: FDA statistical reviewer's analysis

5.3 Ad-hoc OS analysis

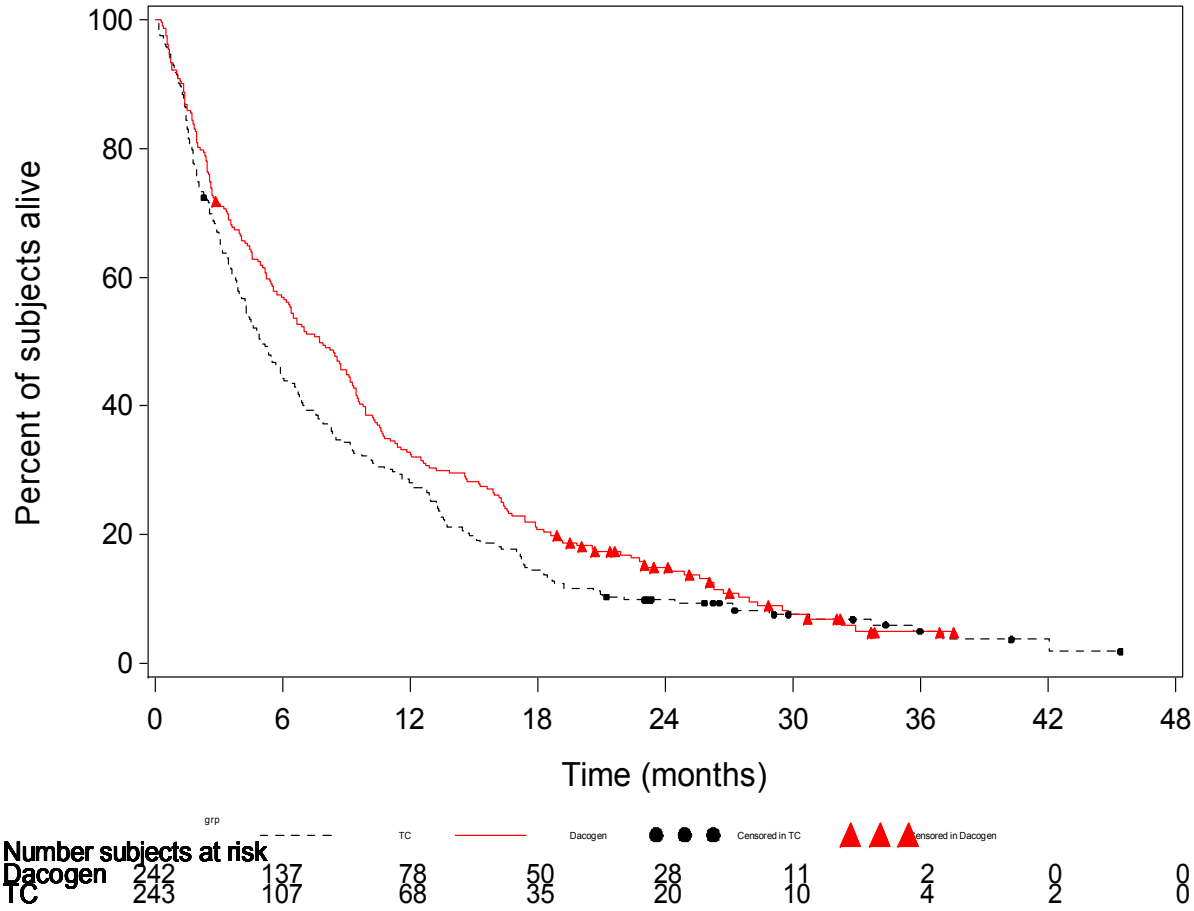
The sponsor performed an ad-hoc OS analysis with a cutoff of October 29 2010. The ad-hoc OS analysis results are summarized in Table 9 and Figure 6.

Table 9: OS – ad-hoc analysis results (Cutoff of October 29, 2010)

	Dacogen (N=242)	TC (N=243)
Death (%)	219 (90.5%)	227 (93.4%)
Median OS (months) (95% CI)	7.7 (6.2, 9.2)	5.0 (4.3, 6.3)
Nominal P-value	0.04	
Hazard Ratio (95% CI)	0.82 (0.68, 0.99)	

Source: sNDA CSR Page #95 Table 23

Figure 3: Kaplan-Meier estimation for OS (ITT, cutoff of October 29, 2010)



Source: Statistical reviewer's figure based on the DACO-016 CSR Page #96 Figure 6.

The nominal "p value" of 0.04 from the ad-hoc analysis is difficult to interpret. Upon failing to achieve statistical significance at either interim analysis or the final analysis, all "alpha" has been spent and any further analyses inflates false positive rate. If there is no true treatment difference and comparisons are done without end and without multiplicity adjustments, a nominal "p-value" less than 0.05 will occasionally occur. Additionally, it was not unlikely to obtain a nominal "p-value" less than 0.05 due to chance at the ad-hoc analysis given the observed OS results at the final analysis. Given the observed hazard ratio of 0.85 at 396 events when the final OS analysis was performed, the probability of obtaining a nominal "p-value" less than 0.05 after 50 additional events is 9.6% if the truth is that Dacogen has no advantage over the TC in OS. Thus, given the results at the final analysis, it was not unlikely to obtain a nominal "p-value" less than 0.05 at the ad-hoc analysis by chance alone. We also note that the probability of obtaining a nominal "p-value" less than 0.05 with 50 additional events is 23.3% if the true hazard ratio is 0.85 (the value for the estimated hazard ratio at the final analysis).

5.4 Secondary endpoints

According to FDA guidance, when the primary analysis fails to demonstrate statistical significance, the secondary endpoints and subgroup analyses are not to be considered for the determination of efficacy. The secondary endpoints based on the statistical analysis plan are summarized as below:

Table 10: Overall remission rate (Cutoff of October 28, 2009)

Remission	**Dacogen N= 242**	**TC N= 243**
CR + CRp, n (%)	43 (18)	19 (8)
CR, n(%)	38 (16)	18 (7)

Source: sNDA CSR Page #99 Table 24.

6. Safety

During the DACO-016 trial, subjects who were randomized to the decitabine arm received decitabine 20 mg/m^2 as a 1-hour I.V. infusion once daily for 5 days every 4 weeks. The subjects who were randomized to the TC arm and did not preselect best care option received cytarabine 20 mg/m^2 subcutaneously once daily for 10 consecutive days every 4 weeks. The dose exposures of study drugs are summarized in Table 11.

Table 11: Dose exposures during the trial (DACO-016)

	Dacogen (N= 238)	**Cytarabine (N=208)**
Median no. of cycles (range)	4.0 (1,29)	2.0 (1,30)
Median treatment duration (range) (months)	4.4 (0.3,29.5)	2.4 (0.1,28.4)
No. of subjects who received ≥7 cycles (%)	91 (38)	40 (19)
Median dose, mg/m^2/week (range)	24 (12, 27)	49 (9,100)

Source: Table 35 CSR page # 134

The safety profiles of studies DACO-016 and DACO-017 are similar to those described in Dacogen label. Treatment discontinuations due to adverse events are shown in Table 12.

Table 12: Treatment discontinuations due to adverse events

	Dacogen (N=238)	**TC (N=237)**
Any AE	237 (100)	231 (97)
Discontinuation of treatment due to AE	90 (38)	96 (41)

Source: Table of 38 CSR Page# 107 & table 47 page # 153

Nearly all subjects received Dacogen or cytarabine experienced at least one treatment emergent adverse event (TEAE) of all grades during the study, compared to subjects received BSC (79%). The top five most common TEAEs that occurred in at least 10% of the subjects were pyrexia, thrombocytopenia, anemia, febrile neutropenia, neutropenia and pneumonia are shown in Table 13.

Table 13: Treatment emergent adverse events of all grades

No. of subjects with TEAEs of at least 10 %	**Dacogen (N=238)**	**Cytarabine (N=208)**	**BSC (N=29)**
Total no. of AEs	237 (100)	208 (100)	23 (79)
General disorders and administration site	193 (81)	162 (78)	16 (55)
- Pyrexia	114 (48)	82 (37)	6 (21)
- Fatigue	33 (14)	28 (13)	3 (10)
- Peripheral edema	50 (21)	40 (19)	2 (7)
- Asthenia	44 (8)	27 (13)	2 (7)
Blood and lymphatic system disorders	183 (77)	145 (70)	9 (31)
- Thrombocytopenia	106 (45)	82 (39)	4 (14)
- Anemia	97 (41)	69 (33)	4 (14)
- Febrile neutropenia	79 (33)	54 (26)	0
- Neutropenia	78 (33)	46 (22)	1 (3)
Infections and infestations	184 (77)	130 (63)	12 (41)
- Pneumonia	58 (24)	45 (22)	5 (17)
- Urinary tract infection	35 (15)	13 (6)	1 (3)
- Oral herpes	25 (11)	16 (8)	0
Gastrointestinal disorders	170 (71)	146 (70)	12 (41)
- Diarrhea	69 (29)	49 (24)	5 (17)
- Nausea	68 (29)	64 (31)	5 (17)
- Constipation	55 (23)	36 (17)	2 (7)
- Vomiting	36 (15)	31 (15)	3 (10)
- Abdominal pain	35 (15)	13 (6)	0
Metabolic and nutrition	136 (57)	89 (43)	11 (38)
- Hypokalemia	63 (26)	39 (19)	5 (17)
- Hypoalbuminemia	41 (17)	21 (10)	2 (7)
- Hypocalcemia	34 (14)	16 (8)	3 (10)
- Hyperglycemia	33 (14)	16 (8)	2 (7)
- Hyponatremia	27 (11)	9 (4)	1 (3)
Respiratory, thoracic and mediastinal	129 (54)	101 (49)	10 (34)
- Cough	52 (22)	37 (18)	3 (10)
- Dyspnea	44 (18)	38 (18)	6 (21)
- Epistaxis	38 (16)	34 (16)	2 (7)
Musculoskeletal and connective tissue	87 (37)	72 (35)	5 (17)
- Pain in the extremity	24 (10)	11 (5)	0
Vascular disorders	81 (34)	56 (27)	5 (17)
Nervous system disorder	80 (34)	64 (31)	6 (21)
- Headache	31 (13)	25 (12)	1 (3)
- Dizziness	17 (7)	23 (11)	2 (7)
Cardiac disorder	70 (29)	57 (27)	6 (21)
Psychiatric disorders	65 (27)	37 (18)	4 (14)
- Insomnia	26 (11)	21 (10)	3 (10)
Renal and urinary disorders	58 (24)	41 (20)	5 (17)
- Renal impairment	22 (9)	17 (8)	3 (10)
Hepatobiliary disorders	56 (24)	33 (16)	5 (17)

No. of subjects with TEAEs of at least 10 %	Dacogen (N=238)	Cytarabine (N=208)	BSC (N=29)
- Abnormal hepatic function	33 (14)	22 (11)	1 (3)
Skin and subcutaneous tissue	91 (38)	60 (28)	6 (21)
- Petechiae	25 (11)	16 (8)	0

Source: sNDA CSR page #139

The most commons Grade 3 and 4 treatment emergent adverse events occurred in subjects were thrombocytopenia, anemia, febrile neutropenia, neutropenia and pneumonia. The incidence of Grade 3 and 4 TEAEs was generally higher among subjects treated with Dacogen comparing to subjects treated with cytarabine. Table 14 summarizes Grade 3 & 4 Adverse Events.

Table 14: Treatment emergent Grade 3 and 4 adverse events

Grade 3 and 4 treatment emergent adverse events	Dacogen (N= 238)	Cytarabine (N= 208)	BSC (N= 29)
No. of subjects with Grade 3 & 4 adverse events	221 (93)	188 (90)	16 (55)
Thrombocytopenia	95 (40)	73 (35)	4 (14)
Anemia	80 (35)	56 (27)	4 (14)
Febrile neutropenia	75 (32)	51 (22)	0
Neutropenia	75 (32)	41 (20)	1 (3)
Pneumonia	45 (19)	31 (15)	3 (10)
Disease progression	36 (16)	39 (18)	2 (7)
General physical health deterioration	30 (13)	33 (16)	5 (17)
Hypokalemia	27 (11)	19 (9)	5 (25)
Pyrexia	24 (10)	16 (8)	3 (10)
Dyspnea	16 (7)	11 (5)	3 (10)
Urinary tract infection	14 (6)	5 (2)	1 (3)
Asthenia	11 (5)	8 (4)	1 (3)
hyponatremia	12 (5)	4 (2)	0
Atrial fibrillation	9 (4)	8 (4)	2 (7)
Hypertension	9 (4)	5 (2)	1 (3)
Abnormal hepatic function	8 (3)	4 (2)	0
Bronchopneumonia	8 (3)	6 (3)	2 (7)
Renal impairment	7 (3)	5 (2)	0

Source: sNDA CSR page #762

7. Issue

The study failed to demonstrate benefit based on statistical interpretation. Given that overall survival is the gold standard, we ask the Oncologic Drugs Advisory Committee to discuss the risks and benefits of Dacogen for the treatment of newly diagnosed AML in patients 65 and older.

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